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"T" Times: Revisiting the Timing of Neuronal Injury in Status Epilepticus

Effects of Epileptiform Activity on Discharge Outcome in Critically Ill Patients in the USA: A Retrospective Cross-Sectional Study

Parikh H, Hoffman K, Sun H, Zafar SF, Ge W, Jing J, Liu L, Sun J, Struck A, Volfovsky A, Rudin C, Westover MB. *Lancet Digit Health.* 2023;5:e495-e502. doi:10.1016/S2589-7500(23)00088-2

Background: Epileptiform activity is associated with worse patient outcomes, including increased risk of disability and death. However, the effect of epileptiform activity on neurological outcome is confounded by the feedback between treatment with antiseizure medications and epileptiform activity burden. We aimed to quantify the heterogeneous effects of epileptiform activity with an interpretability-centred approach. Methods: We did a retrospective, cross-sectional study of patients in the intensive care unit who were admitted to Massachusetts General Hospital (Boston, MA, USA). Participants were aged 18 years or older and had electrographic epileptiform activity identified by a clinical neurophysiologist or epileptologist. The outcome was the dichotomised modified Rankin Scale (mRS) at discharge and the exposure was epileptiform activity burden defined as mean or maximum proportion of time spent with epileptiform activity in 6 h windows in the first 24 h of electroencephalography. We estimated the change in discharge mRS if everyone in the dataset had experienced a specific epileptiform activity burden and were untreated. We combined pharmacological modelling with an interpretable matching method to account for confounding and epileptiform activity-antiseizure medication feedback. The quality of the matched groups was validated by the neurologists. Findings: Between Dec 1, 2011, and Oct 14, 2017, 1514 patients were admitted to Massachusetts General Hospital intensive care unit, 995 (66%) of whom were included in the analysis. Compared with patients with a maximum epileptiform activity of 0 to less than 25%, patients with a maximum epileptiform activity burden of 75% or more when untreated had a mean 22.27% (SD 0.92) increased chance of a poor outcome (severe disability or death). Moderate but long-lasting epileptiform activity (mean epileptiform activity burden 2% to <10%) increased the risk of a poor outcome by mean 13.52% (SD 1.93). The effect sizes were heterogeneous depending on preadmission profile—eg, patients with hypoxic-ischaemic encephalopathy or acquired brain injury were more adversely affected compared with patients without these conditions. Interpretation: Our results suggest that interventions should put a higher priority on patients with an average epileptiform activity burden 10% or greater, and treatment should be more conservative when maximum epileptiform activity burden is low. Treatment should also be tailored to individual preadmission profiles because the potential for epileptiform activity to cause harm depends on age, medical history, and reason for admission.

Commentary

The definition of status epilepticus (SE) has been evolving since it was first introduced in 1964 as "...a seizure [that] persists for a sufficient length of time or is repeated frequently enough to produce a fixed and enduring epileptic condition."[1] The most recent update to the definition and classification of SE was in 2015 by the International League Against Epilepsy (ILAE).[2] In this update, SE is divided into those with prominent motor components and those without a prominent motor component. Status epilepticus with a prominent motor component includes convulsive status epilepticus (CSE) and focal motor SE. Status epilepticus without prominent motor component, also known as nonconvulsive SE (NCSE), includes the types of SE that may be seen in comatose and critically ill patients and also those in which the patient is not comatose, such as absence SE. This update also provided clarity in the duration of seizure activity beyond which it is diagnosed as SE. *Time point t_1* is the time beyond which seizure activity should be regarded as "continuous" and unlikely to stop on its own. This is time at which intervention should be undertaken to stop the seizure. Additionally, *time point t_2* is the time at which ongoing seizure activity results in risk of long-term neurologic consequences.[2] It is the risk of time point t_2 that drives the urgency to treat SE. Time points t_1 and t_2 are different for the

different types of SE. For example, the t_1 for generalized CSE is 5 minutes and t_2 is 30 minutes, while the t_1 for focal SE is 10 minutes and the t_2 is likely greater than 60 minutes.[2]

Unfortunately, the t_1 and t_2 of the most common type of NCSE, that seen in comatose and critically ill patients, is unknown according to the ILAE classification.[2] T_1 is often impossible to determine as the onset of the current altered state is difficult to pinpoint. By default, many consider it to be 5 to 10 minutes. If t_2 could be established for this patient population, it would greatly help clarify how aggressively this condition should be treated.

A recent study by Parikh and colleagues furthers our understanding of t_2 in critically ill patients with electrographic seizure activity.[3] These authors retrospectively evaluated the continuous EEG (cEEG) monitoring records of 995 critically ill patients. They determined the mean and maximum amount of electrographic epileptiform activity (EA) in the first 6 hours of cEEG and compared this to outcomes after accounting for covariates. When the mean EA burden was 2% to 10%, the risk of poor outcome increased by 13.52% compared to those with less than 2% EA. Those with 10% to <30% EA burden had a 17.01% higher risk of worse outcomes, while those with 30% to 100% burden had a 17.97% higher risk. Importantly, the authors included not only electrographic seizures but also lateralized periodic discharges, generalized periodic discharges, and lateralized rhythmic delta activity (LRDA) as EA. Additionally, the authors used pharmacological modelling methods to eliminate the effects of anti-seizure medications on the EA.

Parikh and colleagues also noted that the effect of the EA depended on the underlying etiology of the patient's critical illness. Those with acquired brain injury and hypoxic-ischemic encephalopathy were at more likely to have worse outcomes with higher EA. The authors conclude that patients with a 10% or greater mean electrographic EA burden should be considered for more aggressive treatment, particularly if they have one of the etiologies that poses a greater risk for worsening with EA.

Prior studies have also suggested that electrographic seizure activity can lead to poor outcomes. Critically ill children who have 30 minutes or more of electrographic seizure activity per hour were found to have a higher risk of worse neurologic outcomes and death compared to those who have less than 30 minutes of such activity.[4-6] Another study noted that neurologic decline was more likely if the seizure burden was greater than 20%.[7]

As in children, increasing seizure burden has been shown to worsen neurologic outcomes in adults also. In patients with subarachnoid hemorrhage, the presence of any seizures was associated with worse functional outcomes (81% with unfavorable outcomes) compared to those without seizures (54% unfavorable outcomes).[8] Cognitive outcomes deteriorated as the overall seizure burden increased. The presence of any EA has been associated with worse outcomes in patients with acute ischemic stroke also.[9] In these patients, as the seizure burden increased, the probability of worse outcomes also increased, suggesting a dose relationship between the 2 variables. Additionally, patients with temporal lobe strokes were more likely to have EA than those with strokes elsewhere. Spike frequency of greater than 1.5 Hz may be associated with worse outcomes when analyzed in context of the seizure burden.

How seizure burden is calculated has evolved. In defining SE, most guidelines have included only electrographic seizure activity.[2,10] The study by Parikh and colleagues included not only electrographic seizures but also periodic discharges and LRDA.[3] Despite this relatively broad definition of EA, these authors noted a strong association with neurologic deterioration.

While this study addresses some pressing questions, it raises others. The authors suggest that seizure burden of 10% or greater should merit more aggressive treatment; however, several patients below this cutoff seemed to have neurologic deterioration. The lowest limit of "tolerable" EA remains to be defined. Epileptiform activity beyond simply its presence or absence needs further investigation. The spatial extent of the EA, involvement of specific brain regions, frequency (in Hz) of EEG activity in the EA, the interval between seizures, and other factors related to the EEG findings have not been evaluated in details. All of these may independently impact outcomes.

The 2015 ILAE definition and classification of SE notes that with accumulating research, the definition and classification may need revision.[2] In the near 10 years since its publication, has that time come? The study by Parikh and colleagues is the latest to add to the growing body of evidence that increasing seizure burden leads to worse neurologic outcomes in patients in SE.[3] Increasingly, seizure burden, as a measure EA per hour of cEEG, is being used to define the severity SE. Moreover, while the time point t_2 in NCSE was uncertain in 2015, growing evidence suggests that this may be around 10% to 20% (6-12 minutes per hour). The time point t_2 for other types of SE also bears re-evaluation. Additionally, should the concepts around time point t_1 evolve, especially as it relates to NCSE? Currently, time point t_1 of NCSE is commonly regarded to be between 5 and 10 minutes.[10] This raises the possibility of whether time points t_1 and t_2 could be the same for a particular type of SE, such as NCSE? Finally, should the time points t_1 and t_2 not only depend on the semiology of the SE but also the etiology, with some like acute brain injury being more susceptible to the effects of EA?[3,7] The time is right for another reappraisal of our understanding of SE and how aggressively it should be treated.

Aatif M. Husain, MD, MBA
Department of Neurology,
Duke University Medical Center
Neurodiagnostic Center,
Veterans Affairs Medical Center
Durham, North Carolina

ORCID iD

Aatif M. Husain https://orcid.org/0000-0001-7954-1755

Declaration of Conflicting Interests

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